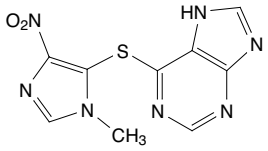
Azathioprine

CAS No. 446-86-6

Known to be a human carcinogen

First listed in the *Fourth Annual Report on Carcinogens* (1985)



Carcinogenicity

Azathioprine is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in humans.

Cancer Studies in Humans

Two large prospective epidemiological studies reported high incidences of non-Hodgkin's lymphoma, skin cancer (squamous-cell carcinoma), connective-tissue tumors (mesenchymal tumors), and cancer of the liver, bile ducts, or gallbladder (hepatobiliary carcinoma) in kidney-transplant patients, who are treated almost routinely with azathioprine and prednisone. Other patients treated with azathioprine (e.g., patients with rheumatoid arthritis, systemic lupus and other collagen disorders, inflammatory bowel disease, and certain skin and renal diseases) also had an increased, although lower, risk of the same cancers as seen in the transplant patients. Rheumatoid arthritis is also a risk factor for non-Hodgkin's lymphoma (IARC 1981, 1982, 1987).

Cancer Studies in Experimental Animals

Evidence for the carcinogenicity of azathioprine from studies in experimental animals is limited. Cancer of the ear duct (squamous-cell carcinoma) was observed in rats orally exposed to azathioprine, and lymphoma was observed in mice exposed to azathioprine by intraperitoneal, subcutaneous, or intramuscular injection. The International Agency for Research on Cancer (IARC 1981, 1982, 1987) considered these results to be inconclusive because of limitations in the study designs and inadequate reporting of these studies.

Properties

Azathioprine is a purine analogue and antimetabolite (an inhibitor of purine synthesis) that exists as pale-yellow crystals at room temperature. It is insoluble in water, very slightly soluble in ethanol and chloroform, sparingly soluble in dilute mineral acids, and soluble in dilute alkaline solutions. It is sensitive to oxidation and decomposes in strong alkali solutions (IARC 1981). Physical and chemical properties of azathioprine are listed in the following table.

Property	Information
Molecular weight	277.3[a]
Melting point	decomposes at 243°C to 244°C[a]
Log K_{ow}	0.1[a]
Water solubility	0.272 g/L at 25°C[b]
Vapor pressure	2.41×10^{-12} mm Hg at 25°C[b]
Dissociation constant (pK_a)	8.2[a]

Sources: [a]HSDB 2009, [b]ChemIDplus 2009.

Use

Azathioprine is an immunosuppressive agent, generally used in combination with a corticosteroid to prevent rejection following allogeneic kidney transplants (i.e., from genetically different donors) and to manage severe cases of rheumatoid arthritis in adults when other treatments have failed. It may also be used following transplantation of other organs and as a second-line treatment for a variety of immunological diseases, such as systemic lupus erythematosus, autoimmune hemolytic anemia, chronic active hepatitis, ulcerative colitis, Crohn's disease, and myasthenia gravis (IARC 1981, IPCS 1996, HSDB 2009).

Production

Azathioprine was first produced commercially in the United States in 1970 and was manufactured by one U.S. company (IARC 1981). In 2009, no U.S. producers of azathioprine were identified (SRI 2009), but it was available from at least nine U.S. suppliers (ChemSources 2009), and five U.S. pharmaceutical companies produced drugs approved by the U.S. Food and Drug Administration containing azathioprine as the active ingredient (FDA 2009). No data on U.S. imports or exports of azathioprine were found.

Exposure

The routes of exposure to azathioprine during medical treatment are ingestion and intravenous injection. Kidney-transplant patients and adults with severe cases of rheumatoid arthritis or other immunological diseases may be treated with azathioprine (IARC 1981). Azathioprine is available in 25-, 50-, 75-, and 100-mg tablets and in injectable form as the sodium salt in 100-mg vials (FDA 2009). The usual dose is 3 to 5 mg/kg of body weight daily for kidney transplant patients, which may be reduced to 1 to 3 mg/kg for maintenance. For rheumatoid arthritis, the initial dose is 1 mg/kg per day, and the dose may be increased to 2.5 mg/kg per day (RxList 2009). In 2008, sales of generic forms of azathioprine totaled $53 million (Drug Topics 2009a). Azathioprine was not among the 200 most-prescribed generic drugs in 2008 (Drug Topics 2009b).

Occupational exposure to azathioprine may occur via inhalation of dust during its manufacture, formulation, and packaging. In a study at a pharmaceutical plant in South Africa, the highest median concentrations of azathioprine dust measured were 0.26 mg/m^3 in the breathing zone and 0.07 mg/m^3 in personal air samples (Jeebhay *et al.* 1993). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 1,849 workers, including 880 women, potentially were exposed to azathioprine (NIOSH 1990).

Regulations

Consumer Product Safety Commission (CPSC)

Any orally administered prescription drug for human use requires child-resistant packaging.

Food and Drug Administration (FDA)

Azathioprine is a prescription drug subject to labeling and other requirements.

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